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PATENT SPECIFICATION

(11) 1 297 080

NO DRAWINGS

(21) Application No. 18388/70 (22) Filed 17 April 1970

(23) Complete Specification filed 19 April 1971

(45) Complete Specification published 22 Nov. 1972

(51) International Classification C07D 31/30

(52) Index at acceptance

C2V 5

C2C 173—198—289 20Y 214 247 250 252 25Y 29X 29Y 30Y 321 323 32Y 351 352 360 361 36Y 431 434 620 650 761 763 790 79Y LD LK

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(54) SALTS OF PYRIDOXINE, HEPTAMINOL AND DIETHYLAMINOETHYLTHEOPHYLLINE

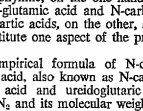
(71) We, SOCIÉTÉ GÉNÉRALE DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES, SOOERAS, a French Body Corporate, of 10 rue Clement Marot, Paris 8e, France, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is concerned with certain novel salts of pyridoxine, heptaminol and diethylaminoethyltheophylline, with a process for preparing them, and with compositions containing them.

It is known to use pyridoxine, heptaminol and diethylaminoethyltheophylline salts, more particularly the hydrochlorides, in the treatment of *inter alia* cardiac, respiratory, neurological and muscular disorders. I have now found that the salts formed between these bases and N-carbamyl-glutamic acid and N-carbamyl-dl- and l-aspartic acids are much more therapeutically active than those used heretofore.

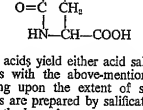
The acid and neutral salts formed between pyridoxine, heptaminol and diethylaminoethyltheophylline, on the one hand, and N-carbamyl-glutamic acid and N-carbamyl-dl- and l-aspartic acids, on the other, are novel and constitute one aspect of the present invention.

The empirical formula of N-carbamyl-glutamic acid, also known as N-carbamoyl-glutamic acid and ureidoglutaric acid, is $C_6H_{10}O_5N_2$ and its molecular weight is 190; its structural formula is:—



The references in this specification to N-carbamyl-glutamic acid are to be taken as referring to the N-carbamyl derivatives of the d-, l- and dl-acids, unless a specific steroisomer is referred to.

The N-carbamyl-aspartic acids are also known as N-carbamoyl-aspartic acids and ureidosuccinic acids; their empirical formula is $C_5H_8O_5N_2$, their molecular weight is 176.1, and their structural formula is:—



These acids yield either acid salts or neutral salts with the above-mentioned bases, depending upon the extent of salification. The salts are prepared by salification of the acids by the bases in an aqueous or alcoholic medium or in dimethylsulphoxide. Advantageously in some cases, salification is carried out at elevated temperature and the resulting salt is left to crystallise; in other cases it is preferable to induce crystallisation of the salt by the addition of an appropriate organic solvent. The crystallised products are separted and then dried, preferably *in vacuo* at from 60 to 80°C.

The present invention also comprises pharmaceutical compositions comprising one of the novel salts and an inert, physiologically acceptable carrier. The novel salts are useful for the treatment of cardiac, respiratory, neurological and muscular disorders. Suitable dosages are from 0.20 to several grams of the active principle, the salt, daily according to the particular salt and the required effect. The salts may be administered in the form of drinkage or injectable solu-

tions, suppositories, tablets, or capsules. In the case of the injectable forms, the salts can be freeze-dried under sterile conditions in a bottle, the latter being accompanied by an ampoule of the injection solvent.

In order that the invention may be more fully understood, the following examples are given by way of illustration only:—

EXAMPLE 1

Pyridoxine N-carbamyl-dl-aspartate (*acid salt*)

17.50 g of N-carbamyl-dl-aspartic acid were mixed with 18 g of pyridoxine base in a beaker. 10 ml of deionised water were added and the mixture was heated to 50°C in a water bath. 100 ml of methanol which had previously been heated to 50°C, were added to the resulting homogenous solution. The solution, which was clear when hot, crystallised on cooling. To ensure complete crystallisation, the solution was left in a refrigerator at from 0 to 5°C for approximately 2 hours. The crystals were separated and dried *in vacuo* at 60°C. Yield: 29 g.

The resulting product was a white crystalline powder which was soluble in water, very slightly soluble in methanol and ethanol, and insoluble in acetone and ether. The pH of a 1% aqueous solution was approximately 4.0.

The pyridoxine base content determined by spectrophotometry was 48.5% on a dry weight basis (theoretical content, 48.8%).

EXAMPLE 2

Pyridoxine N-carbamyl-dl-aspartate (*neutral salt*)

17.50 g of N-carbamyl-dl-aspartic acid were mixed with 36 g of pyridoxine base in a beaker. 10 ml of deionised water were added and the mixture was heated to 50°C in a water bath. 100 ml of methanol, which had previously been heated to 50°C, were added to the resulting homogeneous solution. The solution, which was clear when hot, crystallised on cooling to the laboratory temperature. The crystals were separated and dried *in vacuo* at 60°C. Yield: 50 g.

The resulting product was a white crystalline powder which was very soluble in water, very slightly soluble in methanol and ethanol, and insoluble in acetone and ether.

The pyridoxine base content determined by spectrophotometry was 65.3% on a dry weight basis (theoretical content, 65.7%).

EXAMPLE 3

Pyridoxine N-carbamyl-l-aspartate (*acid salt*).

1.75 g of l-carbamyl-aspartic acid and 1.8 g of pyridoxine base were dissolved in the minimum of water (about 1 ml) in a water bath at 60°C. 20 ml of acetone were added to the resulting homogeneous syrup, the paste formed was ground and allowed to stand at −15°C for one night. The aqueous acetone was then poured off and replaced by 20 ml of fresh acetone, the paste was subjected to further grinding and became solid. The product was then rapidly separated and dried *in vacuo* at 60°C. Yield: 3 g.

The resulting product was a hygroscopic white powder which was very soluble in water, soluble in methanol, slightly soluble in ethanol, and insoluble in acetone and ether.

The pyridoxine base content determined by spectrophotometry was 48.9% (theoretical value, 48.8%).

EXAMPLE 4

Pyridoxine N-carbamyl-l-aspartate (*neutral salt*)

1.75 g of l-carbamyl-aspartic acid and 3.80 g of pyridoxine base were reacted to form the salt as described in Example 3. Yield: 5 g. The resulting product was also hygroscopic and its solubilities were identical to those of the salt of Example 3. The pyridoxine base content was 65.4% (theoretical value, 65.7%).

EXAMPLE 5

Heptaminol N-carbamyl-dl-aspartate (*neutral salt*)

2.2 g of N-carbamyl-dl-aspartic acid were dissolved in about 6 ml of dimethylsulphoxide in a water bath at 50°C, 3.625 g of heptaminol base were added, the solution was left to stand for 10 minutes, and then poured into 20 ml of acetone with agitation. The crystallized product was separated, washed with a little acetone and dried *in vacuo* at 60°C. Yield: 5.5 g.

The product was a white crystalline powder which was soluble in water, methanol and ethanol, and insoluble in acetone, ether and benzene.

The heptaminol base content (potentiometric determination in perchloric acid) was 62.3% (theoretical value, 62.3%).

This product could also be prepared by reaction in water and precipitation by acetone, but crystallisation was more difficult and the yield was less.

EXAMPLE 6

Diethylaminoethyltheophylline N-carbamyl-dl-aspartate (*neutral salt*)

17.6 g of N-carbamyl-dl-aspartic acid and 55.8 g of diethylaminoethyltheophylline were dissolved in 400 ml of ethyl alcohol in a water bath at 50°C. Crystallisation was induced and the solution allowed to stand at −15° overnight. The crystallised product was collected, separated and dried *in vacuo* at 60°C. Yield: 54 g.

The product was a white crystalline powder which was soluble in water and methanol, slightly soluble in ethanol, and insoluble in acetone. The diethylaminotheophylline content determined by spectrophotometry was 75.6% (theoretical value, 76%).

EXAMPLE 7

Diethylaminoethyltheophylline N-carbamyl-l-aspartate (neutral salt)

The procedure of Example 6 was used. Yield 55 g. The appearance and solubilities of the salt were exactly as for the N-carbamyl-dl-aspartic acid salt. The diethylaminoethyltheophylline content was 15% (theoretical value, 76%).

EXAMPLE 8

Pyridoxine N-carbamyl-l-glutamate (acid salt)

19 g of N-carbamyl-l-glutamic acid and 18 g of pyridoxine base were dissolved in 100 ml of hot methyl alcohol. The salt crystallised on cooling to laboratory temperature. The product was separated and dried *in vacuo* at 80°C. Yield: 32 g.

The resulting salt was a white crystalline powder which was soluble in water, slightly soluble in methanol and ethanol, and insoluble in acetone and ether.

The pyridoxine base content determined by spectrophotometry was 46.3% on a dry weight basis (theoretical value, 47%).

EXAMPLE 9

Pyridoxine N-carbamyl-l-glutamate (neutral salt)

19 g of N-carbamyl-l-glutamic acid and 34 g of pyridoxine base were dissolved in 100 ml of hot methanol. The product was left to crystallise by cooling to laboratory temperature and the crystals were separated and dried *in vacuo* at 80°C. Yield: 53 g.

The resulting product was a white crystalline powder which was soluble in water, slightly soluble in methanol and ethanol, and insoluble in acetone and ether.

The pyridoxine base content determined by spectrophotometry was 64% on a dry weight basis (theoretical value, 64%).

EXAMPLE 10

Heptaminol N-carbamyl-l-glutamate (neutral salt)

23.8 g of l-carbamyl-glutamic acid were dissolved in 60 ml of dimethylsulphoxide in a water bath ot 60°C. 36.25 g of heptaminol base were added to the solution, which was allowed to stand for 10 minutes and then poured into 200 ml of acetone with agitation. The crystallised product was separated, washed with a little acetone and dried *in vacuo* at 60°C. Yield: 57 g. The product was a white powder which was soluble in water, methanol and ethanol, and insoluble in acetone, ether and benzene.

The heptaminol base content (potentiometric determination by perchloric acid) was 60.4% on a dry weight basis (theoretical value, 60.5%).

This salt could also be prepared by reaction in water and precipitation by acetone, but crystallisation was more difficult and the yield was lower.

EXAMPLE 11

Diethylaminoethyltheophylline N-carbamyl-l-glutamate (neutral salt)

1.9 g of carbamylglutamic acid and 5.58 g of diethylaminoethylthiophylline were dissolved in 3 ml of water in a water bath at 60°C. The solution was poured into 30 ml of acetone which had previously been cooled to −15°C. The precipitated product was collected and dried *in vacuo* at 60°C. Yield: 5.60 g.

The resulting product was a white powder which was soluble in water, methanol and ethanol, and insoluble in acetone and ether.

The diethylaminoethyltheophylline content determined by spectrophotometry was 73% on a dry weight basis (theoretical value, 74.6%).

WHAT WE CLAIM IS:—

1. A salt formed between pyridoxine, heptaminol or diethylaminoethyltheophylline and N-carbamyl-glutamic acid or N-carbamyl-dl- and l-aspartic acid.
2. The acid and neutral salts of pyridoxine with N-carbamyl-dl-aspartic acid.
3. The acid and neutral salts of pyridoxine with N-carbamyl-l-aspartic acid.
4. The acid and neutral salts of heptaminol with N-carbamyl-dl-aspartic acid.
5. The acid and neutral salts of diethylaminoethyltheophylline with N-carbamyl-dl-aspartic acid.
6. The acid and neutral salts of diethylaminoethyltheophylline with N-carbamyl-l-aspartic acid.
7. The acid and neutral salts of pyridoxine with N-carbamyl-glutamic acid.
8. The acid and neutral salts of heptaminol with N-carbamyl-glutamic acid.
9. The acid and neutral salts of diethylaminoethyltheophylline with N-carbamyl-glutamic acid.
10. A pharmaceutical composition comprising a salt according to any of claims 1 to 9 and an inert, physiologically acceptable, carrier.
11. A process for the preparation of a salt according to any of claims 1 to 9 substantially as herein described in any of the Examples.

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Printed for Her Majesty's Stationery Office by Burgess & Son (Abingdon), Ltd.—1972.
Published at The Patent Office, 25 Southampton Buildings, London, WC2A 1AY
from which copies may be obtained.